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Iron-catalyzed benzylation of 1,3-dicarbonyl compounds by simple toluene derivatives

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An iron-catalyzed oxidative C–C bond formation by the reactions of simple toluene derivatives with 1,3-dicarbonyl compounds is developed. A benzylic radical addition to a benzoylmethanato iron species is proposed for the transformation.

iron-catalyzed, benzylation, toluene derivatives, C–C bond formation

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Direct C–H bond functionalization presents an alternative pathway to traditional functional group transformation in modern organic synthesis [1–5]. The numerous advantages of C–H bond transformation make it highly attractive for chemical synthesis. A great progress for C–H bond functionalization has been made in the past decades [6–15]. However, only a few examples have been reported for the realm of simple sp^3 C–H in the bulky compounds [16–23]. Since toluene derivatives were widely used in chemical industries, pharmaceuticals, and pesticides, it is highly desirable to develop a benzylation method using simple toluene derivatives.

Iron is one of the most abundant elements on earth and attracts much attention due to its low price and low toxicity. Accordingly, iron catalysis has been widely expanded in organic synthesis [24–31], and in particular, iron catalysts have resulted in great advances in the direct oxidation of C–H bonds and C–C bond formation [32–47]. We [48] reported an iron-catalyzed functionalization of benzylic C–H bonds. Powell and coworkers [49] have also developed a conceptually similar, copper-catalyzed, C–C bond formation by oxidative activation of benzylic C–H bonds. However, toluene could not use as a substrate in the former case and exhibits very low reactivity in the latter. Therefore, the extent of reactive benzylic C–H bonds to simple toluene derivatives is one of great challenges in organic chemistry. Herein we wish to report our efforts toward functionalization of simple toluene derivatives using iron catalyst.

1 Experimental

1.1 General information

All reagents were weighed and handled in air and backfilled under N_2 at room temperature. All reactions were conducted under a slightly positive pressure of nitrogen using standard Schlenk line techniques. Unless otherwise noted, all starting materials were commercially available and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded in parts per million (δ) relative to internal standard TMS (0) for $CDCl_3$ and the internal solvent signals (central peak is 77.0 in $CDCl_3$). The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz).

1.2 General procedure for products 3

To a mixture of dibenzoyl methane **1a** (0.5 mmol), toluene **2a** (1.0 mL, 9.0 mmol), and $Fe(OAc)_2$ (0.05 mmol), di-*tert*-

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butyl peroxide (2.0 mmol) was dropped into the mixture under nitrogen at room temperature. The tube was sealed and the resulting mixture was stirred at 120°C for 24 h. The reaction temperature was cooled to room temperature. $K_4Fe(CN)_6 \cdot 3H_2O$ (40 mg), HCl (5%, 3.0 mL), and CH_2Cl_2 (3.0 mL) were added sequentially and stirred until the organic layer turned into colorless. The resulting reaction solution was extracted with 4×5 mL dichloromethane. The extract was washed with 2×10 mL brine and dried over $MgSO_4$. Solvent was evaporated and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether as eluent. **3a** was obtained as colorless oil (61%). ^{1}H NMR δ 7.89–7.87(m, 4H), 7.47(dd, J=7.6, 7.2 Hz, 2H), 7.34(dd, J=8.0, 7.2 Hz, 4H), 7.25–7.17(m, 4H), 7.11(dd, J=7.6, 6.8 Hz, 1H), 5.57(t, J=6.8 Hz, 1H), 3.45(d, J=6.8 Hz, 2H); ^{13}C NMR δ 195.3, 138.9, 135.8, 133.3, 128.1, 128.7, 128.4, 128.4, 126.4, 58.7, 35.1; ATR-FTIR (cm^{-1}): 3064, 3038, 2907, 1694, 1667, 1595, 1497, 1350, 1271, 1236, 1182, 1001, 930, 758, 694, 608, 515; MS(EI) m/z(%): 317(M^+), 209, 149, 131, 105, 91, 77(100), 65, 51, 41, 37; HRMS(ESI) calcd. for $C_{22}H_{18}NaO_2$(M^++Na): 337.1199; found: 337.1196.

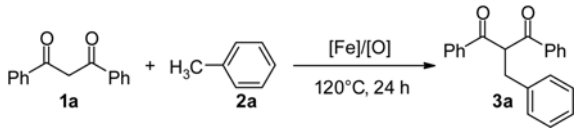
2 Optimization of the reaction conditions

Dibenzoyl methane **1a** and toluene **2a** were chosen as the model substrates and *tert*-butyl peroxide, $(t\text{-BuO})_2$, was used as the oxidant to investigate the suitable reaction conditions (Table 1). The desired product **3a** was obtained with 41% yield in the presence of 2 equiv of $(t\text{-BuO})_2$ (Table 1, entry 1). The yield of **3a** was improved to 64% when 4 equiv of oxidant were applied (Table 1，entry 2). Importantly, the present transformation did not proceed at 80°C (Table 1, entry 3), while reactive benzyl derivatives afford the corresponding oxidative coupling products smoothly [48]. The efficiency of this reaction dramatically decreased when 5 mol% of catalyst was used (Table 1, entry 4). Other organic peroxides were ineffective (Table 1, entries 5–7). Although $FeCl_3$ led to a slight low yield of **3a**, comparable yields were obtained when $FeBr_2$, $Fe(OAc)_2$, $Fe(acac)_2$, $Fe(acac)_3$ and $Fe_2(CO)_9$ were used as catalyst (Table 1, entries 8–13). Interestingly, **3a** was formed with 12% yield even in the absence of iron catalyst (Table 1, entry 14). Moreover, TEMPO, a radical trapping reagent, completely suppressed this reaction (Table 1, entry 15). These results indicated that a radical intermediate is most likely involved in the initial steps of the present transformation.

3 The scope of the reactions

The scope of the present transformation was investigated under the optimized reaction conditions (Table 2). *para*-Xylene afforded the desired oxidative product **3b** smoothly

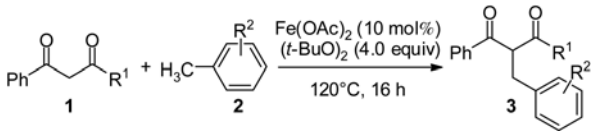
Table 1 Optimization of the reaction conditions[a)]



Entry	[Fe] (mol%)	[O] (equiv)	Yield (%)[b)]
1	$FeCl_2$ (10)	$(t\text{-BuO})_2$ (2)	41
2	$FeCl_2$ (10)	$(t\text{-BuO})_2$ (4)	64
3	$FeCl_2$ (10)	$(t\text{-BuO})_2$ (4)	N.D.[c)]
4	$FeCl_2$ (5)	$(t\text{-BuO})_2$ (4)	21
5	$FeCl_2$ (10)	PhCOOO-*t*-Bu (4)	9
6	$FeCl_2$ (10)	*t*-BuOOH (4)[d)]	8
7	$FeCl_2$ (10)	$(PhMe_2CO)_2$ (4)	23
8	$FeCl_3$ (10)	$(t\text{-BuO})_2$ (4)	49
9	$FeBr_2$ (10)	$(t\text{-BuO})_2$ (4)	66
10	$Fe(OAc)_2$ (10)	$(t\text{-BuO})_2$ (4)	72(61)
11	$Fe(acac)_2$ (10)	$(t\text{-BuO})_2$ (4)	67
12	$Fe(acac)_3$ (10)	$(t\text{-BuO})_2$ (4)	67
13	$Fe_2(CO)_9$ (5)	$(t\text{-BuO})_2$ (4)	62
14		$(t\text{-BuO})_2$ (4)	12
15	$Fe(OAc)_2$ (10)	$(t\text{-BuO})_2$ (4)	N.D.[e)]

a) Conditions: **1a** (0.5 mmol), **2a** (1.0 mL), under N_2; unless otherwise noted. b) NMR yields are determined by ^{1}H NMR using CH_2Br_2 as an internal; the isolated yield is given in the parenthesis. c) Not detected by ^{1}H NMR; 80°C. d) 5.5 mol/L in decane. e) Not detected by ^{1}H NMR; TEMPO (1.0 mmol).

Table 2 The representative results[a)]



Entry	R^1	R^2	**3**	Yield (%)[b)]
1	Ph	Me	**3b**	81(71)
2	Ph	*m*-Me	**3c**	65(62)
3	Ph	*o*-Me	**3d**	45(42)
4	Ph	3,5-di-Me	**3e**	58(49)
5	Ph	*p*-Br	**3f**	64(58)
6	Ph	*p*-I	**3g**	71(64)
7	Ph	*p*-OCOMe	**3h**	64(57)
8	Ph	*p*-COMe	**3i**	47(42)
9	Ph	2-Naphthyl	**3j**	64(60)
10	Ph	*p*-Me, *o*-Br	**3k**	60(54)[c)]
11	Ph-4-Me	*p*-Me	**3l**	76(74)
12	Ph-4-Br	*p*-Me	**3m**	78(74)
13	Me	*p*-Me	**3n**	62(57)
14	OEt	*p*-Me	**3o** (R^1=OEt) **3o'** (R^1=O-*t*-Bu)	57(51) 18(12)

a) Conditions: **1** (0.5 mmol), **2** (1.0 mL), under N_2; unless otherwise noted. b) NMR yields are determined by ^{1}H NMR using CH_2Br_2 as an internal; the isolated yield is given in the parenthesis. c) The 1∶1 regioisomers.

(Table 2, entry 1). However, *meta*- and *ortho*-xylene gave the corresponding products **3c** and **3d** with a decreasing yield compared with *para*-xylene (Table 2, entries 2 and 3). Moreover, a moderate yield of **3e** was obtained when mesitylene was applied (Table 2, entry 4). These results indicated that the steric effect affected the efficiency of the reactions. Halogen and ester groups tolerated the present conditions and transformed into the desired products efficiently (Table 2, entries 5–7). In contrast, electron-withdrawing group decreased the yield of the reaction dramatically (Table 2, entry 8). This result suggested that the electronic effect also plays an important role. 2-Methyl naphthalene was a suitable substrate and the desired product was isolated in good yield (Table 2, entry 9). 2-Bromo-1,4-dimethylbenzene led to two regioisomers **3k** with a 1∶1 ratio (Table 2, entry 10). Other aromatic 1,3-diketones reacted efficiently with *para*-xylene (Table 2, entries 11 and 12). A 62% yield of **3n** was obtained when 1-phenylbutane-1,3-dione was used (Table 2, entry 13). β-Ketoester is unstable under the present reaction conditions and the transesterification product **3o**' was obtained together with the desired product **3o** (Table 2, entry 14).

4 Mechanistic studies

In order to assess the nature of charge development in the transition state of the reaction, a Hammett study was conducted by the relative reactivity of substituted toluenes (Figure 1). The Hammett slope ρ was determined to be –0.31 for the reaction of dibenzoylmethane with substituted toluenes. The negative sign of ρ reflects the fact that electron-donating substituent on the aromatic ring increase the reaction constant. On the other side, the small absolute value of ρ often means that the mechanism of the reaction involves radical intermediates. Moreover, a linear correlation of $\lg k/k_0$ vs σ implies that the position of the transition state is not changing as a result of a changing substituent.

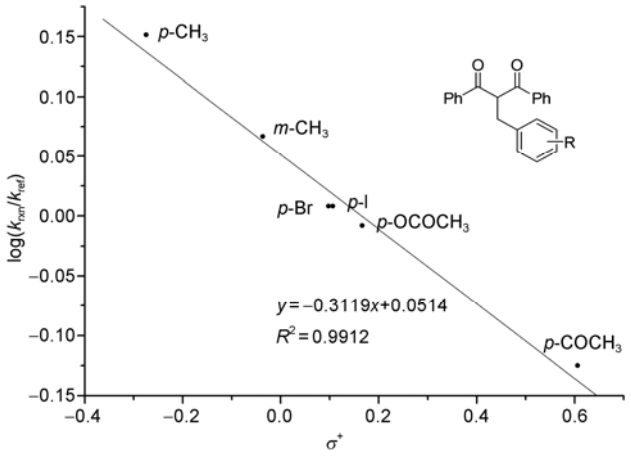
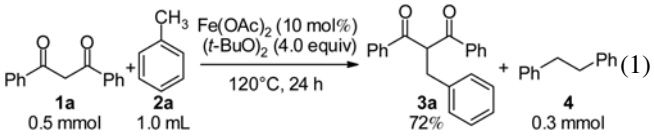
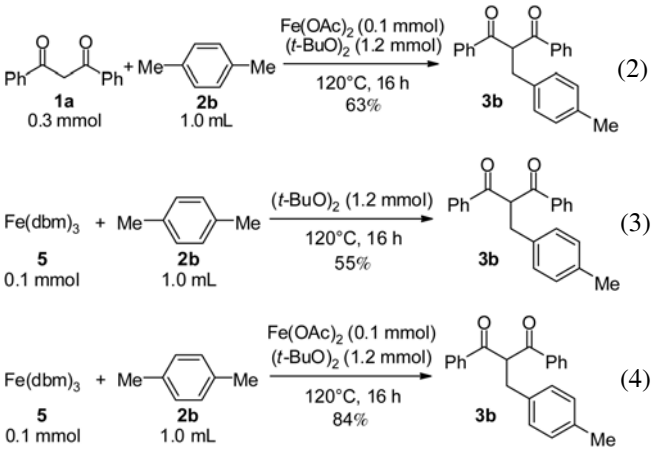


Figure 1 A Hammett plot.

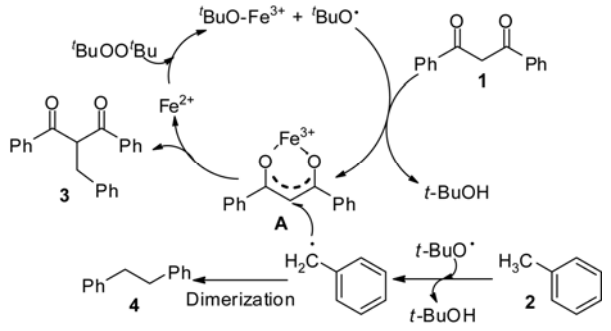
Importantly, a certain amount of 1,2-diphenylethane **4** was obtained under the standard condition (eq. (1)). This result strongly supports a benzyl radical involving in the present transformation [50]. Furthermore, the competitive kinetic isotopic effect (KIE) experiments were carried out under the standard reaction conditions. The reaction shows a k_H/k_D=8.0±0.1. This significant isotopic effect indicates that the C–H bond cleavage is the rate-determinating step of this transformation.



The roles of iron catalyst were also investigated (eqs. (2)–(4)). A 63% yield of **3b** was obtained in the presence of one third equiv of $Fe(OAc)_2$ related to **1a** (eq. (2)). Interestingly, a comparable yield was obtained using tri (dibenzoylmethanato) iron **5**, $Fe(dbm)_3$, instead of **1a** in the absence of $Fe(OAc)_2$ (eq. (3)). These results indicated that the formation of benzoylmethanato iron is likely involved in the present reaction. Importantly, the combination of $Fe(dbm)_3$ **5** and $Fe(OAc)_2$ increased the yield of **3b** to 84% (eq.(4)), which is similar to the result of entry 1, Table 2. The result demonstrated $Fe(OAc)_2$ will also improve the efficiency of benzylic C–H bond cleavage. Therefore, iron catalyst plays two roles in the present transform: (i) as a Lewis acid to activate 1,3-dicarbonyl substrates; (ii) as a redox catalyst to promote the decomposition of peroxide and thus improve hydrogen abstraction from benzylic C–H bond.



Based on the above results, a tentative mechanism for the iron-catalyzed functionalization of toluene derivatives is proposed (Scheme 1). *tert*-Butyl peroxide, $(t\text{-BuO})_2$, decomposes into *tert*-butoxyl radical and oxidizes Fe^{2+} to Fe^{3+}. Then, a benzoylmethanato iron intermediate **A** is formed via a ligand exchange. On the other side, hydrogen abstraction by *tert*-butoxyl radical affords a benzylic radical, which is supported by the formation of 1,2-diphenylethane **4**. The radical addition of the benzylic radical to **A** followed by ferric oxidation provides the desired coupling product **3**.



Scheme 1 A tentative mechanism.

Overall, the Fe^{2+}-Fe^{3+} redox processes play key roles in the present C–C bond formation, which are the reductive homolytic cleavage of O–O bond in the peroxide and the oxidation of the carbon radical to oxonium.

5 Conclusions

In summary, we developed an iron-catalyzed oxidative coupling of simple toluene derivatives with 1,3-dicarbonyl compounds. The mechanistic studies demonstrated that the reactions proceed via a benzylic radical addition to a benzoylmethanato iron species. The applications of iron catalyst and simple toluenes are the advantages for organic synthesis.

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